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Review Article

Updates in diagnosis and management of osteoporosis in postmenopausal women

Wickramasinghe WWMHWJB[1], Wanasinghe WMMPB[2], Lanerolle S[3]

[1] *Acting Consultant Obstetrician and Gynaecologist, Base Hospital, Meerigama*[1]

[2] *Resident Obstetrician and Gynaecologist, Teaching Hospital, Peradeniya*[2]

[3] *Consultant Obstetrician and Gynaecologist, CSHW*[3]

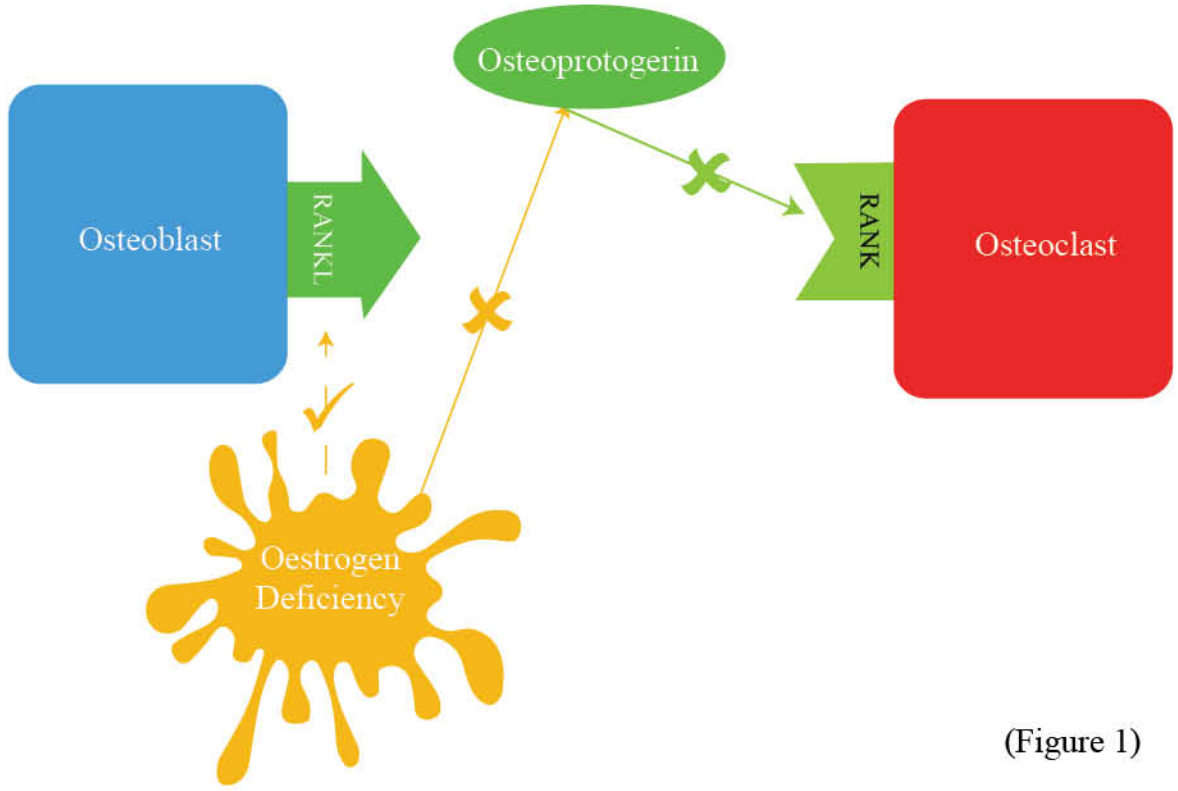
Corresponding Author *- Dr. Wickramasinghe WWMHWJB*

Introduction

WHO defines osteoporosis as "a progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue with consequent increase in bone fragility and susceptibility to fracture". Osteoporosis is becoming a global health concern as recently the World Health Organization study group estimated over 75,000,000 individuals being affected in USA, Japan and Europe alone.[1] This has led to a significant financial burden as well. In fact, osteoporosis related fractures account for more morbidity than Myocardial infarctions in developed countries.

Pathophysiology

Bone remodeling is a cyclical process made up of four stages, Activation, Resorption, Reversal and Formation. During activation, osteoclasts are activated on the bone surfaces. This will be exaggerated in the absence of oestrogen hormone at menopause. thereby, leading to increase bone resorption during the next phase. However, there is no concurrent increase in osteoblastic activity during the Formation phase. This unbalance is termed "uncoupling" during menopause which ultimately lead to bone loss.[2]



(Figure 1)

The molecular process of above, is now well understood. The receptor activator of nuclear factor kappa B ligand (RANKL) which is bound to osteoblasts will be released under influence of oestrogen deficiency and then binds to receptor activator of nuclear factor kappa (RANK) on the surface of osteoclasts. This would promote osteoclasts activity in bone resorption.[3] Meanwhile, osteoprotegerin (OPG) compete for the same receptor and once occupied, cease progression of the process. OPG is stimulated by oestrogen as well. This RANK-OPG balance is lost with reduction in serum oestrogen levels.[4](Figure 1)

Diagnosis

According to WHO diagnosis of osteoporosis is based on Dual-energy X-ray absorptiometry (DXA) scan (Table 1), of which DXA of the femoral neck is the most preferred. Spine should be avoided, as it would provide a false increased BMD in those with osteoarthritis and degenerative changes.

	BMD T score
Normal	+2.5 to -1
Osteopenia	-1 to -2.5
Osteoporosis	<-2.5
Severe Osteoporosis	<-2.5 with 1 or more bone fragility fracture

(Table 01)

Despite the high accuracy of using DXA Bone Mineral Density (BMD), in diagnosing Osteoporosis, advancing age has few other clinical risk factors which could influence the risk of bone fractures. Hence, the Centre for Metabolic Bone Disease at Sheffield introduced "WHO Fracture Risk Assessment Tool" (FRAX), which gives the probability of an individual to develop fractures in the subsequent 10-year period.[5] (Figure 2)

Prevention of Osteoporosis

Life style advices including increased physical activity with regular weight bearing exercises, causation of smoking and moderation of alcohol consumption can minimize risk of osteoporosis.

Furthermore, falls prevention strategies should be implemented in elderly population, by optimizing their eye sight, improving balance and minimizing environmental hazards with risk of falling can further minimize fractures.[2] (Table 2)

Pharmacological treatment

Treatment should be offered to those with osteoporotic fractures, BMD T score of <-2.5 and those with BMD T score of -1 to -2.5 with FRAX risk of 20% or more.[5] Types of treatment can be broadly classified into Anti resorptive agents and anabolic agents.

Bisphosphonates

These act by binding to the bone surface and inhibiting farnesyl pyrophosphate synthase enzyme which is required for the formation of the osteoclast cytoskeleton, thus preventing bone resorption. Oral preparations are preferred as first line. However, for those who are intolerant, IV preparations are offered.

Calculation Tool

Please answer the questions below to calculate the ten years probability of fracture with BMD

Country : Sri Lanka Name/ID : About the risk factors

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: Date of Birth: Y: M: D:
2. Sex Male Female
3. Weight (Kg)
4. Height (Cm)
5. Previous Fracture No Yes
6. Parent Fracutred Hip No Yes
7. Current Smoking No Yes
8. Glucocorticoids No Yes
9. Rheumatoid arthritis No Yes
10. Secondary osteoporosis No Yes
11. Alcohol 3 or more units/day No Yes
12. Femoral neck BMD (g/cm²)

Select BMD

Clear Calculate

Weight Conversion

Pounds → kg

Convert

Heught Conversion

Inches → cm

Convert

00015103

Individuals with fracture risk assessed since 1st June 2011

Risk	FRAX fracture risk	Managementre
Low risk	<10%	Life style advice Daily total calcium intake of 1200mg Daily Vitamin D 800IU[6]
Moderate risk	10-20%	Life style advice Daily total calcium intake of 1200mg Daily Vitamin D 800IU Medication considered in those with additional risks (corticosteroid use, fractures, aromatase inhibitors use, etc.)
High risk	>20%	Pharmacological treatment

(Table 02)

The HORIZON-PFT trial showed a reduction of vertebral fractures by 70% and hip fractures by 41% in those treated with zoledronic acid.[7]

The Fracture Intervention trial showed an efficacy of 47% and 51% in reducing vertebral and hip fractures respectively in patients treated with alendronate.[8] FLEX trial further analyzed long term use of Alendronate vs discontinuing treatment after 5 years and found that continuing therapy significantly reduced the risk of vertebral fractures.[9] Other commonly used bisphosphonates are mentioned in the table (Table 3).

Hormone replacement therapy (HRT)

As explained above, oestrogen promotes osteoblasts activity while reducing the lifespan of osteoclasts. This promotes a positive bone balance and therefore is considered first line option in preventing osteoporosis. Women Health Initiative (WHI) showed a significant reduction in vertebral and hip fractures among HRT users.[10] Furthermore, earlier the HRT is commenced following menopause, better the results as majority of bone loss occurs during the first three to four years following menopause.[11] A meta-analysis of 57 trials

Anti-resorptive agents	Anabolic agents
HRT	Strontium (Discontinued)
Bisphosphonates *Oral* Alendronate 5/10mg daily Risedronate 5mg daily Ibandronate 2.5mg daily Etidronate *IV* Zoledronic acid 5mg yearly Ibandronic acid	Teriparatide Abaloparatide
SERM (selective estrogen receptor modulator)	
TSEC (Tissue Selective Estrogen Complex)	
Denosumab 60mg SC/6 monthly	
Romosozumab	
Calcitonin *(Discontinued)*	

(Table 03)

Despite their efficacy, these group of medication has their own set of adverse effects like GI intolerability, muscle pains, transient hypocalcaemia and less than 1% oral absorption rate. Recent evidence suggests there could be an increased risk of jaw osteonecrosis and atypical femoral fractures. In order to minimize these effects, a "drug holiday" can be implemented.

demonstrated that there is an increase in BMD by 6.8% in the hip and 4.1% in the hip in post-menopausal women who were treated with estradiol for two years period.[12] Similar results were shown in the HOPE trial where multiple doses of conjugated equine oestrogen with medroxyprogesterone acetate were compared against placebo and showed an increase in BMD in all groups.[14]

When concerning the safety in use of HRT, a secondary analysis of WHI data by age group revealed that significant increased risk of myocardial infarction (MI), venous thrombo embolism and stroke were only seen in the age group above 70 years, not the younger women. In fact, in women following less than 10 years of menopause, there was a reduction in rates of MI.[15]

Combination of HRT with Bisphosphonates has been shown to be more effective than either of the medication used alone. Studies have been done with multiple combinations including alendronate, risedronate and calcitriol with conjugated equine oestrogen, and all of these showed a higher gain in BMD than single agent.

Selective Estrogen Receptor Modulators (SERM)

Commonest SERM used in treatment for osteoporosis is Raloxifene, which has shown to reduce vertebral fractures. A meta-analysis showed that raloxifene increased the BMD by 1.8% and 2.1% of the lumbar spine and hip respectively. However, their benefit in reducing hip or non-vertebral fractures are yet to be proven. MORE trial showed that in addition to prevention, raloxifene is also effective in treating patients with established osteoporosis. The study compared raloxifene against a placebo in treating women with osteoporosis and found a 30% reduction in fracture rates.[16]

Bazodoxifene, a third generation SERM, is proven to be effective in preventing all type of fractures as opposed to raloxifene. Lasofoxifene, another third generation SERM, has a higher bioavailability and has a 10 times higher affinity to oestrogen receptors compared to raloxifene.

The main advantages of using SERM are that it does not cause endometrial hyperplasia and they have a potent anti-estrogenic action on the breast.

Tissue Selective Estrogen Complex (TSEC)

Coupling of conjugated oestrogen with a SERM forms a TSEC and has shown to be effective than Raloxifene or placebo while minimizing the risk of endometrial hyperplasia as opposed to using oestrogen alone.[18]

Denosumab

Denosumab is a monoclonal antibody which binds to RANKL, inhibit osteoclast differentiation and induce apoptosis. Denosumab is considered a second line treatment for these who do not show a satisfactory response to bisphosphonates.[19] FREEDOM trial, which compared Denosumab with placebo showed an increase of 9.2% and 4% BMD in lumbar spine and hip respectively. Furthermore, vertebral fractures were reduced by 68% while non-vertebral fractures reduced by 20%.[20] FREEDOM extension trial showed that the crossover of the previous placebo group gained a significant BMD.[21] However for those who were given long term denosumab, similar side effects to bisphosphonates were seen including osteonecrosis of jaw and atypical fractures.

Romosozumab

Romosozumab is another monoclonal antibody which has shown promising results in FRAME trial, where a 75% reduction in vertebral fractures were noted over placebo.[22]

Teriparatide

Teriparatide is a recombinant human parathyroid hormone, which has an anabolic effect on bones.[23] NICE recommends its use as a second line treatment option in those who cannot tolerate or show a satisfactory response to bisphosphonates. In Fracture Prevention trial, who were treated with daily subcutaneous teriparatide, BMD was increased by 9.7% in low dose (20mcg) group and by 13.7% in high dose (40mcg) group. Teriparatide is licensed only to be used for 2 years duration as longer use large doses could lead to osteosarcoma. Unfortunately, the effect of teriparatide, quickly drops once treatment is discontinued. Therefore, a consolidation therapy with an alternative medication need to be offered.[24] Cost of treatments is another limitation and therefore, treatment is reserved for those with high risk of osteoporotic fractures.

Recent multi-center double blinded RCT showed that combination of teriparatide with Risedronate resulted in substantial increase in BMD in those with severe osteoporosis.[25]

Abaloparatide

Synthetic analog of parathyroid hormone related peptide, which has an anabolic action on bones is a newer medication which has shown to reduce vertebral fractures by 86%.[26]

Calcitonin

200 IU of salmon calcitonin (Which is forty times more potent than human calcitonin) was found to reduce spine fractures by 33%. ORACAL study showed a significant increase in lumbar spine BMD in oral calcitonin group while no significant effect was seen on nasal spray group.[27] However there are recent concerns in increased risk of malignancies among users of calcitonin and therefore is no longer a recommended treatment option.

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